INHALATION THERAPY WITH ANTIBIOTICS

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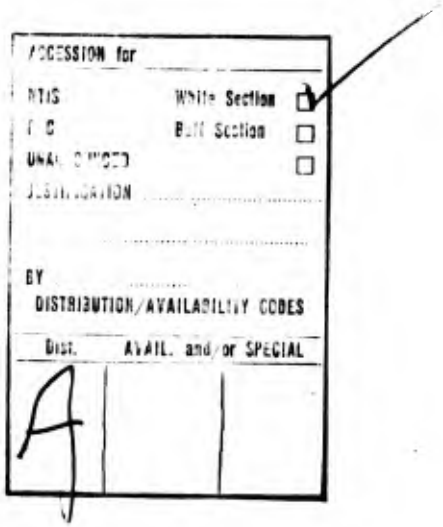
Many problems are created in the antibiotic therapy of bacterial exacerbation in cases of chronic bronchitis. One of these problems, no doubt, is the recidivism, which invariably follows the end of the antibiotic effect within a period of time. The non-purulent interval between two recidivisms is called the relapse rate. On the one hand, there are close relations between the relapse rate and the functional state of the bronchial mucous tissues which exhibit powerful defensive mechanisms in the healthy state. However, the mucous membranes are damaged functionally and morphologically to such an extent in the advanced state of the disease that they are no longer capable of providing natural resistance against subsequent reinfection. On the other hand, there are interesting relations between the relapse rate and the composition, dose, and administration mode of the antibiotic used. Thus, the infection-free interval provides some information on the economic aspects of a given preparation. The relapse rate is shortest after treatment with tetracyclin preparations; it is much longer after treatment with chloramphenicol, cephalosporin, and

ampicillin; for a long time it has been the most impressive after administration of the combination preparation Trimethoprim + Sulfamethoxazol. It is now superseded by Amoxycillin. There is an obvious relationship between the length of the infection-free interval and the dose given (bactericidal + bacteriostatic).

The obvious question now is about the antibiotic interval prophylaxis. The test reports available on the subject are contradictory. The consensus appears to be that it is advisable to refrain from administering antibiotics for prophylactic purposes. A weighty argument for this recommendation is the observation that there are only sub-optimal and hardly measurable amounts of the systemically given antibiotic in the mucous tracheo-bronchial secretion, so that the usefulness of such a treatment is not entirely proven.

If this is the situation, one may ask whether higher antibiotic activity in the tracheo-bronchial secretion can be accomplished by inhalation of the antibiotic; this should manifest itself clinically by the lengthening of the relapse rate. While being fully aware of the often-cited concerns (resistance development, sensitization, losses in the aerosol device, inadequate distribution, deposition and penetration of the aerosol in the bronchial tree) -- which are overexaggerated and are relatively less important in the case of strong indication -- we sought practical confirmation:

After successful conclusion of a systemic treatment of purulent exacerbation in a case of chronic bronchitis with Trimethoprim + Sulfamethoxazol (480 + 2400 mg/day orally during five days; Bactrim®), the patients (19 in number) inhaled a solution of the same preparation twice daily with the aid of an electric inhalator (64 mg + 320 mg/day, using the Pari-Inhalierboy instrument) until recidivism. A second group of 19 patients, comparable in terms of mucous membrane damage and after the same systemic pretreatment, received blank inhalations twice a day through the same instrument for comparison. In the first group, which inhaled active substance, recidivism appeared only after 34 days, while in the second group, which inhaled blank material, only 18 days elapsed before the onset of recidivism. This difference is statistically highly significant, and proves that inhalation of antibiotics is a theoretically feasible way for infection prophylaxis.



AEROSOL THERAPY OF CHRONIC BRONCHITIS WITH KANAMYCIN

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Infection loci developed in the course of chromic bronchitis require treatment with various antibiotic formulations, which are usually administered perorally or parenterally. The bronchial and peribronchial changes that generally develop make penetration difficult and reduce the effectiveness of the perorally or parenterally administered antibiotics (E. Krieger, 1970). In order to prevent bronchial infection in such cases, all researchers (H. Dennig and N. Wagner, 1970; H. Lode, 1970; E. Krieger, 1970; O. P. Schmidt, 1970; W. Nitscheff and Iw. Dikanaroff, 1971) employed with success inhalation of antibiotics such as Rifocin, Nebacetin, Bacitracin, chloramphenicol, tetracyclin, etc.

On the basis of these literature references and of our own studies dealing with the aerosol treatment of respiratory infections, we decided to elucidate the possibilities of the use of Kanamycin inhalation in the therapy of exacerbated chronic bronchitis. Our observations were made on 70 patients with exacerbated chronic bronchitis, including 38 women and

32 men. Nine suffered from common chronic bronchitis, 6 from pus-forming bronchitis, 24 from obstructive bronchitis, 19 from asthma-like bronchitis, and 12 from deforming bronchitis. Most patients were over 40 years old. Extensiv clinical, functional, biochemical, and microbiological examinations were made on the patients before and after the aerosol treatment. The microbiological examination of the sputum showed the sensitivity of the isolated bacterial flora to Kanamycin to be 68; the resistance was 2. Bacteriological examination of the excretion was made of 25 patients, using the Mulder method. Considering the severity of the inflammation process, we administered 1-3 times daily between 0.250 to 0.500 g Kanamycin. It was inhaled from a solution in 4 ml distilled water. Only those patients were included in the study who showed negative allergy test results for this antibiotic. In the case of most patients (53) 2-5 drops of Alupent, Aludrin, or Isoprenalin -- dissolved in 2 ml Bisolvon or Mucosolvin -- was inhaled two to four hours prior to the application of the Kanamycin aerosol. This is desirable if we wish to attain maximum bronchial and mucolytic effect and to ensure deep penetration of the antibiotic into the respiratory tract. The inhalation was accomplished with the aid of the TUR USI-2 ultrasonic aerosol instrument (in some tests we used the USI-3 model). The duration of the aerosol treatment was 20 days for 14 patients and more than 20 days for the others. Sole inhalation therapy was followed with 10 patients; the others

received a combination therapy with simultaneous peroral or -- in some instances -- parenteral antibiotic or sulfonamide administration.

The following clinical results were obtained after the end of the Kanamycin inhalations: Cessation of the cough in 36 patients (52.2%), cessation of expectoration in 32 (49.2%), disappearance of the breathing difficulties in 31 (65.9%), cessation of the feel of pressure in the chest in 16 (88.8%), and normalization of the temperature in 18 (72.0%). The number of patients with purely slimy expectoration increased by approximately one-third; only two patients (6.4%) continued to have pussy expectoration with slimy. No patient had only pussy expectoration. The number of patients with secreted amounts of up to 10 ml in 24 hours increased more than two-fold. The number of patients with expectorate of 11 to 20 ml in 24 hours decreased to one-third, and not a single patient (out of 27) showed secretion amounts of more than 20 ml. Tachypnea was eliminated in 10 patients (71.4%) out of a total of 14; cyanosis or lividity of the lips was eliminated in 4 patients (80.0%) out of a total of five. Undesirable knock echos from the lungs (mainly attenuated vesicular breathing with delayed expiration) was eliminated in 40 patients (66.7%) out of a total of 60, who had this at the beginning of the therapy. The respiration noises (moist or dry wheeze) disappeared in 41 patients (63.1%) out of a total of 65. The respiration functional values, which were pathological in 55 patients before the aerosol therapy, changed as follows: the vital

capacity improved in 41 patients (74.5%), the respiration impact value (Tiffenau test) improved in 40 (72.8%), the breathing limit value improved in 42 (76.3%), and the bronchial air resistance improved in 41 (74.5%). The initially measured values varied at the beginning of the treatment. Changes were also observed in the following laboratory test data after the end of the inhalation therapy: The blood sedimentation reaction became normal in 23 patients (60.5%), the number of leucocytes became normal in 15 (60.0%) out of 25 patients with initial leucocytosis; the differences in the differential blood pattern disappeared in 7 patients (58.3%) out of a total of 12; the serum instability problems disappeared or the pectinograms became normal in 7 patients (70.0%) out of a total of 10 and in 6 patients (66.7%) out of a total of 9. The bacteriological sputum tests after aerosol therapy showed the following changes: Absence of Pneumococci in 41 patients (95.4%) out of a total of 43 with positive bacteriological results before the treatment, disappearance of Haemophylus influenzae in 18 (60.0%) patients out of a total of 30, disappearance of Staphylcocci in 25 (92.5%) out of a total of 27, disappearance of Streptococci in 19 patients (95.0%) out of a total of 20, and disappearance of the mixed bacterial flora in 8 patients (88.8%) out of a total of 9 with initially positive bacteriological results. Only in a few patients did we encounter resistance in the isolated Staphylococci against Kanamycin.

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No patient exhibited allergic or toxic side effects of the severity that would have necessitated termination of the therapy. This is a difference between Kanamycin and other antibiotics, of which the inhalative administration often causes allergic reactions (P. Imperato et al, 1964; H. Lode, 1970; V. Böhlau, 1972).

Our clinical studies demonstrate the feasibility of aerosol treatment for patients afflicted with exacerbated chronic bronchitis. At the same time, the therapeutic results obtained enable us to reach the following conclusions:

1. Aerosol treatment of exacerbated chronic bronchitis with Kanamycin, alone or in combination with other antibacterial agents, is a means for eliminating the clinical symptoms of the affliction, for normalizing the physical pulmonary parameters, for improving the bacteriological health of the sputum, and for improving the respiratory functional values in most patients.

2. The inhalation of broncholytic and secretolytic agents before the use of the Kanamycin is desirable to ensure deeper penetration of the antibiotic into the respiratory tract.

3. Kanamycin inhalations are tolerated well by the patients, and they cause no allergic or toxic reactions of the kind that would necessitate termination of the aerosol treatment.

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POSSIBILITIES AND LIMITATIONS OF ANTIBIOTIC THERAPY BY MEANS OF AEROSOLS

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The main areas of application for aerosol therapy are and remain to be in cases of pulmonary and bronchial diseases, with cases of chronic, unspecific lung diseases predominating. However, asthma of the bronchi also often require antibiotic inhalations. The expected result of the inhalation therapy is based on the resorptive and the local effects of the antibiotics inhaled; bronchial ectasias represent a particularly fruitful area. Since in such cases the blood circulation of the bronchial walls is usually inadequate, one of the most useful aspects of the aerosol therapy is that it supplements the administration of expectorants and other physical measures, especially in view of the fact that it is difficult to ensure that the antibiotic enters the blood stream. Aerosol therapy enables us to bring the medication to the site of the disease so that it can exert its action right there. We shall dispense here with the theoretical details and refer to the papers of Dirnagl in this connection.

Pulmonary mycoses require regular aerosol therapy also, especially since almost all antimycotically effective substances must be administered parenterally or enterally only with the greatest caution. This applies particularly to Amphotericin B, which -- when used in the treatment of lung mycoses or for states of irritation -- proved to be useful by controlling the candial flora in the bronchial tree in the form of inhalation. Pulmonary mycoses of the severe kind often definitely require general therapeutic measures also; this, however, does not reduce the significance of aerosol therapy.

Pulmonary fibroses and pneumoconosias also respond to long-term therapy with aerosols, as does mucoviscidosis in children. For these reasons, one cannot agree with the statements of Medici, who regards aerosol therapy within the framework of pulmonary and bronchial diseases as useless and of no therapeutic value.

The significance of bacterial infection as the cause for the triggering and exacerbation of chronic, unspecific pulmonary diseases has been confirmed by numerous epidemiological, clinical, and bacteriological studies. Even if, as a rule, the bacterial infection is only a secondary affliction , its further course is of major significance for the outlook of the disease.The disease-causing agents identifiable in the sputum or the bronchial secretion are not speficically bronchial pathogens in the chronic, unspecific lung diseases in most cases. In most cases they represent secondary invaders of an already damaged bronchial

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mucous membrane. The primary factors that lead to damage of the bronchial wall are usually other types, mainly exogenic noxia, atmospheric pollution, irritating gases, and -- last but not least -- tobacco smoke and particularly viruses deposited on the mucous membrane of the respiratory tract. All these can then cause damage.

The effect of chemotherapy in the bronchial tree depends on the sensitivity of the micoorgans against the chemotherapeutic agent. Although hemophilic influenza and Pneumococci are and remain in the forefront of the disease-causing agent spectrum in chronic, non-specific pulmonary diseases, at least in Germany there is a slow but steady rise of poorly treatable germs in the sputum flora. Foremost among these are coliform agents, Proteus, and -- last but not least -- Pseudomonas aeruginosa.

The chemotherapeutic problem of therapy for the chronic, non-specific pulmonary diseases is becoming greater as time goes on, mainly because of the emergence of penicillinase-resistant Staphylococci. This sometimes complicates the therapeutic approach and makes it necessary to use effective medications parenterally and perorally.

There is no doubt about the fact that parenteral or oral administration of high doses of bactericidal substances is highly important in cases of severe exacerbation of the chronic bronchitic state. In this paper it is not possible to discuss all therapeutic possibilities in detail; they range from Penicillin G through its semi-synthetic derivatives

to the combination of Sulfamethoxazol and Trimethoprim as well as the relatively new antibiotics from the group of the amineglycosides.

Antimicrobial measures may be applied intermittently, but sometimes there is a need for long-term therapeutic measures, mainly in the case of hereditary defects such as homo- or heterozygotic alpha-1-antitrypsin deficiency or immunoglobulin deficiency. It is ar established fact that all chemotherapeutic agents and antibiotics perform better in bronchial infections in the acute state when applied perorally or parenterally than when applied by inhalation. Antibiotics should be administered in the form of aerosol in cases where this represents part of a long-term therapeutic measure with the simultaneous use of bronchial dilating agents, and where there are destructions in the bronchial tree area, so that one must assume the existence of diffusion or penetration difficulties for perorally administered antibiotics.

Penicillin and its derivatives, as well as streptomycin may no longer be used as aerosols since they may cause hypersensitivity in short time, and even anaphylactic states may be triggered by them. The same misgivings exist in connection with almost all water-soluble small-molecular antibiotics. Inhalation of such substances merely seals the passage for subsequent measures administered perorally or parenterally; this is a significant hazard for the patient. The semi-synthetic penicillins such as ampicillin, oxa-, cloxa-, and carbenicillin are such substances.

The broad-spectrum antibiotics such as chloramphenicol and tetracyclin -- with the exception of thiamphenicol -- are the most suitable for inhalation, preferably in conjunction with a mucolytic agent such as Fluomycetin A; they, however, gained no large foothold in aerosol preparations. The main reason for this is poor solubility and in many instances unpleasant taste. Sulfonamides were tried earlier in the form of aerosols; however, they are no longer employed in this manner.

At the present time, only those antibiotics which have a relatively large molecule are used for inhalation; these are not resorbed because of the size of their molecules. They are substances which have risks in parentaral administration but are well tolerated. For such purposes we recommend neomycin in conjunction with bacitraci· Tyrothricin, .olymyxin E, Nystatin, and Amphotericin B, especially the latter, .n cases of pulmonary mycoses or the occurrence of Candida albicans in the bronchial flora following broad-spectrum antibiotic therapy. Gentamycin we found, is also suitable for use in the aerosol form. The Gentamycin molecule is obviously not suitable as a haptene because of its molecular size.

The present thought about the usefulness of inhalation antibiotic therapy is that it supports the previously damaged bronchial mucous membrane in its defensive reaction, thereby also promoting the expectoration

of stagnating secretions. Reinfection can be prevented in this manner, and in some instances one may even dispense with otherwise necessary long-term therapeutic measures using peroral medication -- which may always introduce the risk of side effects.

Since more than 50% of all physicians have inhalation equipment today, these remarks are intended to convey the recommendation that they should remove antibiotic inhalation measures from their list of treatments in cases of acute, pussy states wherever possible, since such instances represent clear indications of peroral or parenteral therapy. An inhalation therapy with aerosols is undesirable also in cases of severe, acute bronchial obstructions where no intermittent above-pressure respiration is possible. Such therapy always promotes alveolar ventilation, mechanical bronchi dilatation, correction of distribution difficulties, and cleansing of the bronchial system. Intermittent above-pressure treatment requires medical supervision only in the beginning. Thereafter, intelligent patients will readily learn the use of the equipment and the manner in which it is adaptable to their specific needs.

More than 40% of all patients aged 50 years or above, who must undergo surgery, suffer of some chronic respiratory syndrome; since, however, all narcotics -- irrespective whether injected or inhaled -- and all muscle relaxants restrict ciliary activity and respiratory activity, inhalation treatments of a prophylactic character are very important today.

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Inhalatory application of surface antibiotics became more important in pre- and postoperative conditions in addition to inhalations of indifferent substances. Here also, as in all indications of aerosol use, it is important to have the upper respiratory tract unobstructed and all lung sections adequately ventilated to permit the administered aerosol to penetrate. Most ventilation difficulties are attributable to obstructions, and only a few -- 10-15% as a rule -- to restrictions; thus, the added application of bronchial spasmolytic agents becomes very useful in the aerosol therapy with surface antibiotics also.

It is also important to sterilize and maintain the inhalation equipment used in above-pressure respiration. Disease-causing agents may deposit in them -- including resistant variants of the gram-negative type. Bacterial tests should be performed periodically, with cultures.

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TOXICOLOGICAL AND PHARMACEUTICAL STUDIES ON RATS AFTER REPEATED INHALATION OF GENTAMYCIN AEROSOL

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In broncho-pneumonal diseases, the effects of orally administered or injected antibiotics must often be supplemented by inhalative local therapy (Schmidt and Krieger, 1971). Gentamycin, which proved to be suitable against highly resistant disease-causing agents of many types (Wahlig, 1966), begins to become important in this area as more and more problem-causing gram-negative germs are encountered. No hypersensitivity phenomena were observed so far with Gentamycin inhalation (Orth and Bopp, 1971; Regula et al, 1972). After it was demonstrated that injected Gentamycin is identifiable in the bronchial secretion (Wieser et al, 1972), clinical studies were also made to establish the resorbability of inhaled Gentamycin by determination of the antibiotic concentration in the serum and the urine (Regula et al, 1972; Regula et al, 1973). We conducted animal

experiments on this subject, where it was our aim to establish whether Gentamycin in aerosol form would irritate the respiratory tract. We used high doses in terms of general toxicological aspects; thus, it became obvious that we might also analyze the serum and tissue concentrations and examine any systemic side effects.

Materials and methods

Test animals

Rats, Wistar-AF/HAN/EMD, weighing 140 g at the beginning of the experiments, maintained two in a Makrolon cage Type III, fed with Altromin-R ad libitum.

Aerosol generation and exposure of the rats

A 1% aerosol of Gentamycin was prepared in the commercial Pari-Primus instrument; the aerosol was supplied to the atomizer by means of an infusion pump. Purified compressed air was supplied to the instrument at a pressure of 1.5 atm (gauge pressure). The emerging air flow had a rate of 12 liters/minute. A total of 27.5±0.5 ml solution was aerosoled per hour. The atomizer was connected to an opening in a cylindrical chamber modified according to Niessen et al (1963) at the center of the bottom. The tips of 20 tubular cages for rats reached into the chamber, so that the animals had to breathe the aerosol coming from the top and the bottom, without being whole-body exposed in the process.

Droplet-size distribution in the aerosol

The average diameter of the droplets was found to be 1.9 µm, using an Unico 4-stage cascade impactor (Lippmann, 1961) for the measurement. In addition, aerosol samples were sprayed onto a green membrane filter. Counting of the generally spherical crystalline deposits under a top-illumination dark field showed that 86% of the Gentamycin particles was < 1 µm and 100% was < 5 µm.

Gentamycin concentration in the breathing air

This was determined gravimetrically with membrane filters. The sample size was 10-12 liters, aspired at the rate of 3 liters/minute. In addition to weighing, the amount of Gentamycin deposited on the filters was determined microbiologically also. On the basis of 39 measurements, the average Gentamycin concentration in all tests was found to be 539±41 mg/m^3.

Microbiological determination of Gentamycin

The determination was carried out according to the modified agar diffusion test as described by Grove and Randall (1955), using Bacillus subtilis ATCC 6633 as the test microorganism.

Animal experiments

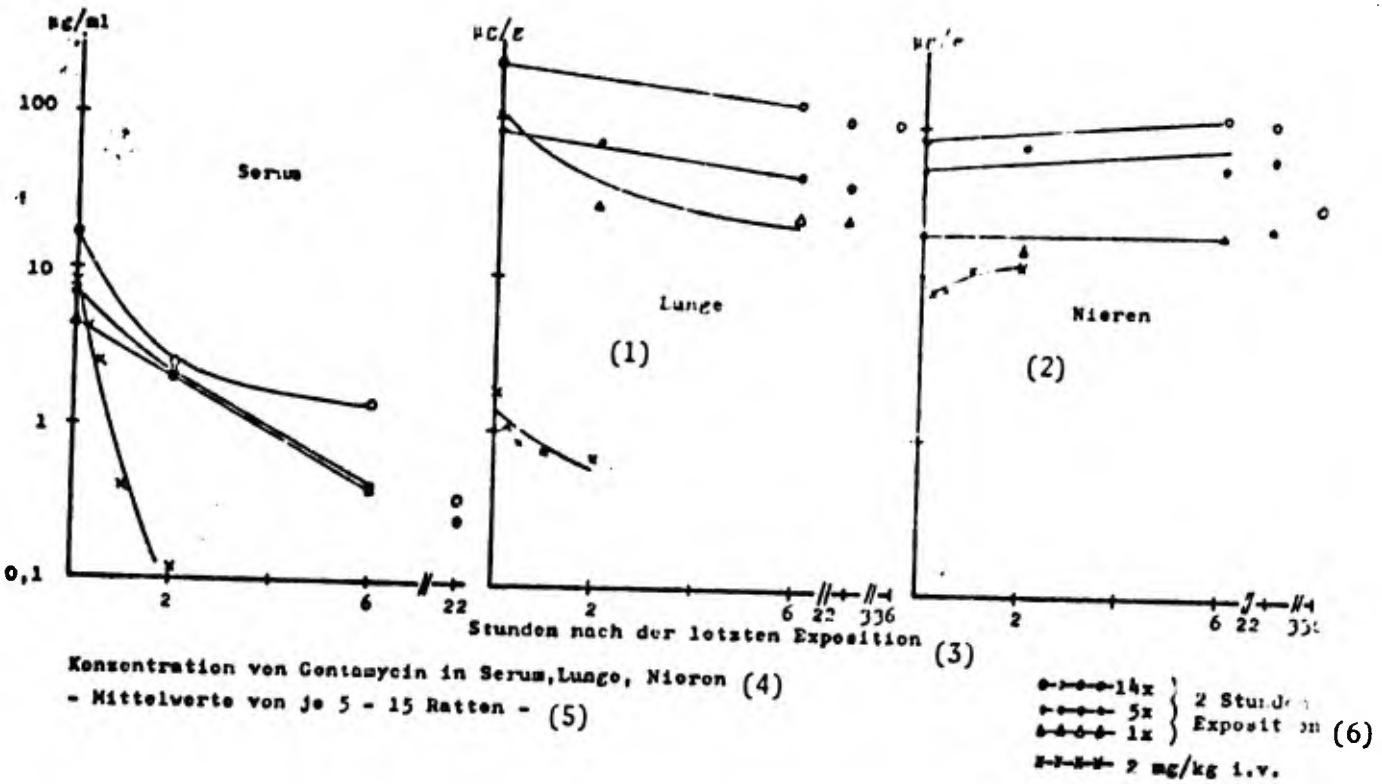
Four groups of 10-20 rats each were exposed for two hours each day for one day, five consecutive days, or 14 consecutive days. The 14-times exposed animals and a large number of control animals (who were exposed

under identical conditions to water aerosol) were killed (some immediately after the last exposure and some eight days thereafter) and dissected. Their organs were weighed and examined histologically, with the respiratory tract -- prepared after special technical processing -- being in the forefront of interest. The remaining animals, as well as three additional groups of animals (10-20 rats each, exposed for 0.5, 1, and 2 hours, each) were used in the pharmacokinetic studies. The times of blood sampling, and removal from their lungs, kidneys, and livers are seen in the illustration.

Results and discussion

The twice-daily exposure for a period of 14 days caused no noticeable or audible irritation phenomena in the rats used in the test. The significant decrease in the respiratory frequency compared to the controls might have been triggered reflectorially by the effect of the aerosol (Ulrich and Haddock, 1972). There were no histological indications of an irritation effect in the trachea or the lungs. The level of tracheal and bronchial epithelium was not reduced. Number, shape, and distribution of the beaker cells were normal, and the cilia appeared to be intact. In evaluating these findings one must take into consideration the fact that the Gentamycin concentration during clinical inhalation is below 539 mg/m^3, and that the patients are not exposed to the inhalation for more than about 15 minutes, so that in a comparison between humans and less sensitive rats there has been compensation by means of higher

concentration, longer exposure duration, and higher exposure frequency. The good tolerance of Gentamycin aerosol in children (Truckenbrodt et al, 1972) and adults (Orth and Bopp, 1971) confirms the findings of the animal experiments.



(1) Lung; (2) Kidneys; (3) Hours after the last exposure; (4) Concentration of Gentamycin in the serum, the lungs, and the kidneys; (5) Average values for 5-15 rats; (6) Two-hour exposure

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Fodder consumption and increase in body weight were not affected by the exposure. The organ weights were normal. No pathologic changes were found in the histological examinations. Specifically, there were no differences between the rats exposed to Gentamycin and the control rats with respect to kidneys and inner ears.

The toxicological significance of these results is unquestionable if we evaluate the serum and tissue concentrations. It can be seen from the illustration that considerable amounts of Gentamycin were resorbed by the rats from the breathing air. The concentration in the lungs, in the serum, and in the kidneys was approximately proportional to the number of exposures. The highest concentration was 230 µg/g in the lungs, from which Gentamycin was released rapidly during the first few hours after the last exposure, and thereafter at a very slow rate. The initially rapid concentration decrease might be attributable to Gentamycin dissolved in the traceo-bronchial mucus which was subsequently swallowed, while the reduced release rate indicates retention of the antibiotic in the pulmonary parenchyma. With the diffusion from the lungs, the concentration in the kidneys increased during the first 24 hours. The increase became bigger as more and more Gentamycin was retained in the lungs. One can estimate from the difference in the kidney concentrations after a single exposure and 14 exposures how the concentration developed during the two-week test period.The absence of histopathological changes in those kidneys in which

a high concentration level was maintained over a long period of time is worthy of special mention.

Very low overall concentration levels were found in the liver; the concentrations were in all cases lower than those prevailing at the same time in the serum.

Concentrations that are therapeutically effective in humans were reached in the serum of rats even after a single exposure; however, these concentrations prevailed for short periods of time only. The concentrations dropped rapidly in each experiment. The rate of decrease increased with decreasing amounts of Gentamycin present in the lungs. While the concentration decreased exponentially after a single intake, the rather clear two-phase course of the elimination curves after repeated intake is likely to be attributable to diffusion of Gentamycin from the lungs.

In order to be able to interpret the concentration level in the serum, we applied Gentamycin intravenously. The illustration shows that after five inhalations the same concentration was attained in the serum as after injection of a dose which is therapeutically effective in humans.

The dose pulmonally resorbed by the rats was, on the basis of the Gentamycin concentration in the breathed air, the duration of the inhalation, the minute respiration volume of the rats, and an estimated respiration rate of 30%, approximately 13 mg per kg of body weight. It should be noted, however, that in the clinic approximately 0.1 mg

per kg body weight is resorbed plus an injected dose of 1 mg per kg body weight, if we start from a single test-person inhalation and the amounts of Gentamycin secreted in the urine (Regula et al, 1973).A comparison of these figures and the high serum concentration level found in the rats as a result of the large doses permits drawing the conclusion that clinical determination exists for the unquestionable feasibility of Gentamycin inhalation (Regula et al, 1972) on the basis of animal experiments.

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INHALATION THERAPY WITH GLUCOCORTICOSTEROIDS.

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Soon after their discovery, corticosteroids were remarkably successful in the therapy of obstructive diseases of the respiratory tract. These results, and the considerable side effects of long-time oral therapy with corticosteroids, soon suggested attempts for a local therapy with corticosteroid aerosols. The aim of these attempts was to attain an increased active-ingredient concentration in the bronchial system which permitted the use of so low pressures that no or only reduced systemic side effects usually encountered in long-term corticosteroid therapy develop.

Glucocorticosteroids have an anti-exudative effect, and they are capable of reducing the swelling of exudatively afflicted tissues. There is a decrease in sputum volume and sputum viscosity under the effect of corticosteroids [17]. On the other hand, corticosteroids have no spasmolytic effect on the bronchial musculature. Nor is there evidence for an

effect on the β-receptor stimulating substances in tne bronchi [7]. On the other hand, there is evidence that persons afflicted with asthma who had been treated with glucocorticoids show a lesser experimentally triggered acetylcholine or histamine bronchial spasm than before treatment with corticosteroids [10, 13]. It is possible that the corticosteroids in this instance affect an allergic antigen-antibody reaction, and prevent the liberation of histamin from the mastocytes [10] and thus the development of a bronchial spasm and branchiolar edema. According to current views, the main therapeutic effect of corticosteroids in the treatment of obstructive respiratory tract syndromes is the swelling of mucous membrane and decrease of sputum quantity and viscosity. It is also possible that they have an antispastic effect in cases where they have been administered before the triggering of an allergic bronchial spasm.

This is the background for the inhalation therapy with glucocorticosteroids: this is an "interval therapy" which prevents the onset of an asthma attack and also improves the obstructive syndrome by reducing the swelling of the mucous membrane and reduction of mucus production. Decreasing the viscosity of the bronchial secretion may also exert a beneficial effect on the ventilatory function. The more pronounced is the obstructive syndrome in general, and the bronchial-wall edema in particular, the more beneficial the effects of corticosteroid therapy are likely to be.

During the asthma attack itself, this effect is obtained in the best and fastest manner by intravenous administration of the corticosteroid, since only this ensures that the substance reaches the bronchiolar mucous membrane during an attack also. Objective reports on the results attainable with corticosteroid inhalation therapy are very infrequent in the literature. In one experiment, hydrocortisone succinate was found to be relatively ineffective, perhaps because of its high resorption rate. Questionable effects with hydrocortisone acetate and prednisolone acetate were also reported [10]. Good results were reported for the inhalation therapy with Dexamethasone esters [1, 2, 5, 7, 8, 9, 15].

We gathered our own experience in inhalations of a suspension of Dexamethasone isonicotinate crystals, having a particle size of 4. Dexamethasone isonicotinate does not dissolve readily in water and is therefore resorbed slowly [3, 16].It should be mentioned, however, that there was some evidence of resorption -- mainly through the stomach after swallowing -- and reduction of the plasmacortisole level in this therapy also [12]. The Dexamethasone was administered in the form of a dosing aerosol, using 2-3 squirts 3-4 times a day over a period of four weeks. In order to obtain objective comparison values, we determined the effects of an isoprenaline aerosol for all patients before the corticosteroid-aerosol therapy, and compared the results of the former with those

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of the four-week corticosteroid inhalation period. At the day during which the final functional test was carried out, the patients had no more inhaled so as to exclude any immediate inhalation effect from the functional evaluation. The results of these experiments are presented in Figures 1 to 4.

It can be seen that the effect is best in the case of a true bronchial asthma. In cases where the chronic-obstructive emphysema predominates, the effects of the corticosteroid inhalation therapy are the weakest. Chronic obstructive bronchitis shows an intermediate effect. The effect of corticosteroid inhalation is the most pronounced in patients who have eosinophilic cells in the sputum or the tracheal swab (Figure 5).

Figure 6 shows the functional values of a 45-year old patient afflicted with bronchial asthma and considerable obstructive ventilation difficulty apart from the asthma attacks. The values are shown for the situation preceding and following a four-week inhalation therapy with corticosteroids. The improvement of the endobronchial difficulties is quite pronounced, as indicated by improvement of the resistance.

The differences in the therapy results for various kinds of the obstructive syndrome show how important it is for the therapeutical considerations to distinguish between an asthma that predominates among the obstructive symptoms and an obstructive emphysema. In the case of bronchial asthma, inhalation therapy with Dexamethasone has a good effect, and the

effect is minimal in cases of obstructive emphysema.

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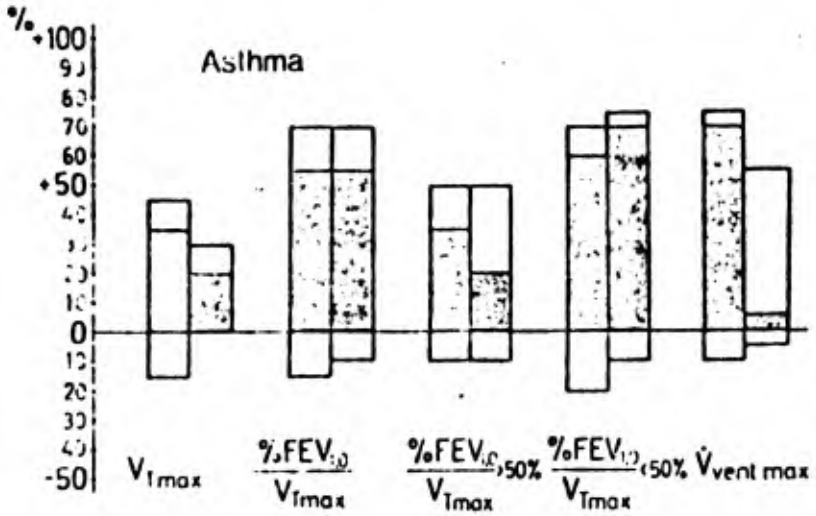

Figure 1. Effect of a four-week treatment with a glucocorticosteroid aerosol, compared with that of an isoprenaline aerosol, on 20 patients afflicted with bronchial asthma. The left column in each column pair shows the effect of the corticoid aerosol; the left, that of the isoprenaline aerosol. Changes of less than 10% of the starting value were disregarded. Changes of more than 20% are marked by striation. Above the abscissa: percent values of the improvements; below, the worsenings.

V_{Tmax} denotes vital capacity; $\%FEV_{1.0}/V_{Tmax}$ denotes relative capacity per second; $V_{vent\ max}$ denotes respiration limit value. For relative capacity per second the cases were examined with a starting value of less than 50% (severe obstruction) and above 50% (slight obstruction) separately

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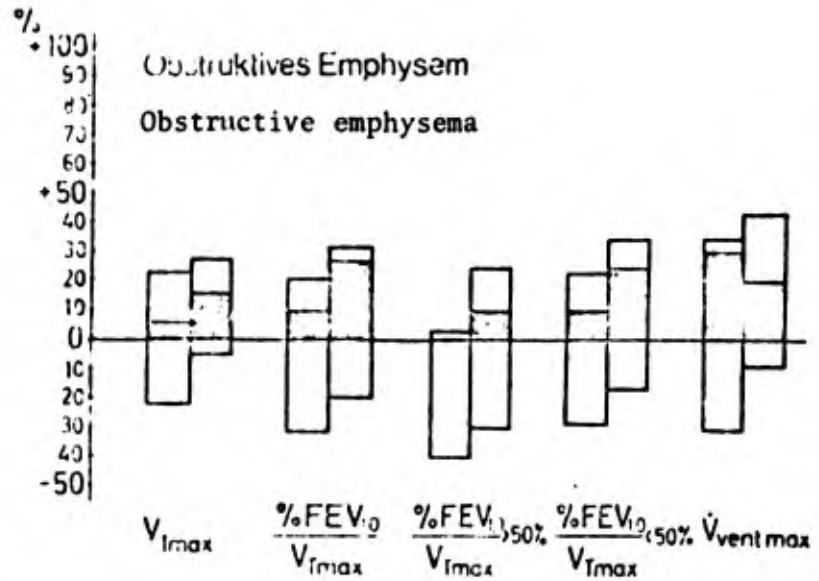

Figure 2. Effect of a four-week treatment with a glucocorticosteroid aerosol, compared with that of an isoprenaline aerosol in 45 patients afflicted with obstructiveemphysema (for details see Fig. 1)

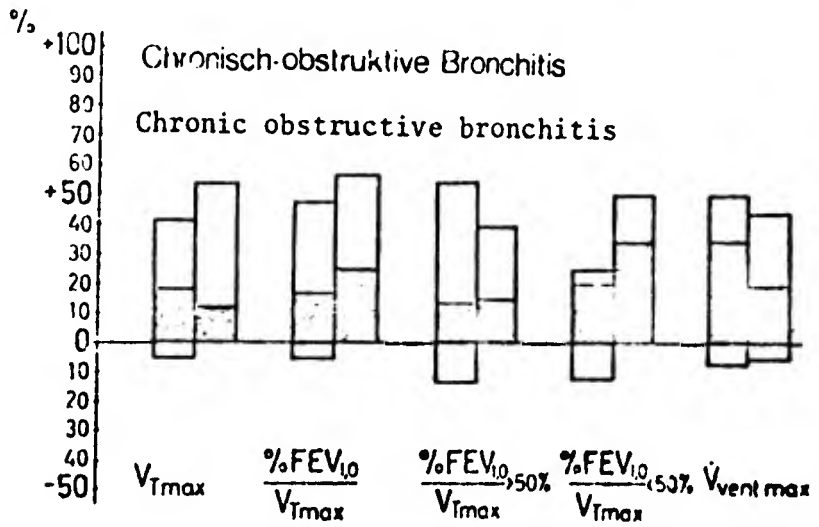

Figure 3. Effect of a four-week treatment with a glucocorticosteroid aerosol, compared with that of an isoprenaline aerosol in 76 patients afflicted with chronic obstructive bronchitis (for details, see Figure 1).

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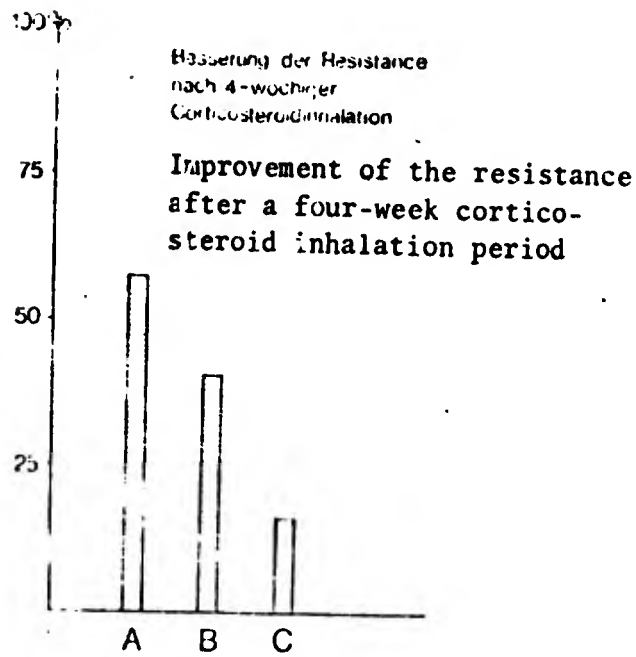
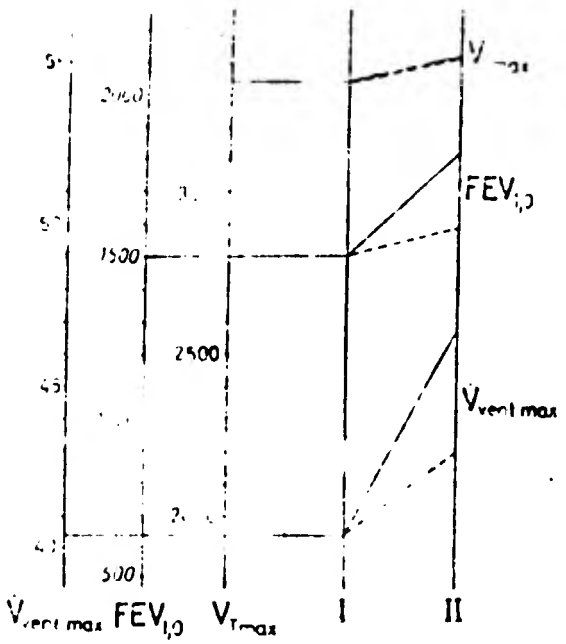


A = Bronchial asthma (n = 20)

B = Chronic obstructive bronchitis (n = 76)

C = Obstructive emphysema (n = 45)

Figure 4. One can see from these resistance data how much better the effect of glucocorticosteroid inhalation is on patients afflicted with bronchial asthma than on those afflicted with chronic obstructive bronchitis or obstructive emphysema



——————— Dexamethasone-21-isocyanate

---------- Isoprenaline

Figure 5. Patients afflicted with eosinophilia in the sputum or trachea swab (n = 19)

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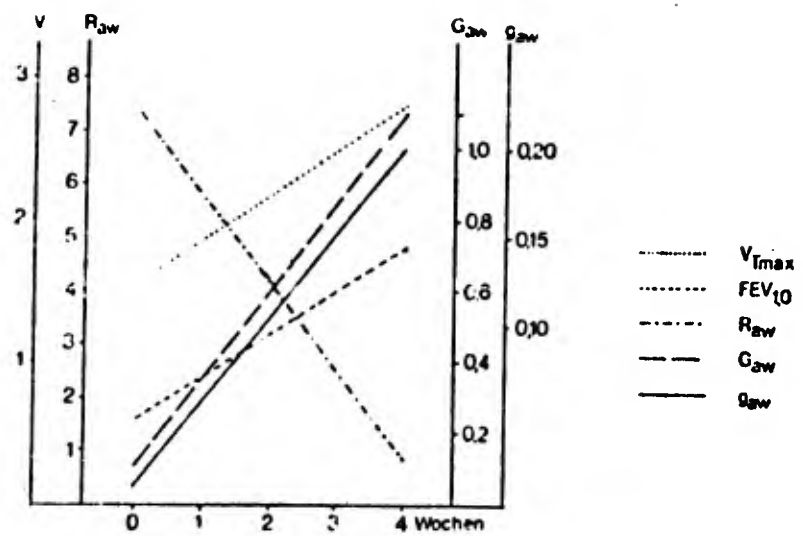

Figure 6. Changes in vital capacity (V_{Tmax}), secondary capacity ($FEV_{1.0}$), resistance (R_{av}), conductance (G_{aw}), and specific conductance g_{aw}) in a 45-year old patient afflicted with bronchial asthma under inhalation therapy with glucocorticosteroids

Wochen = weeks

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